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Adrenergic
Beta-Receptor Blockers,
Adrenalin and
Intraocular Pressure

by
Arne Öhrström

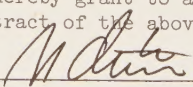
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Adrenergic Beta-Receptor Blockers, Adrenalin and
Intraocular Pressure

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Abstract The interaction between adrenergic beta-receptor blockers (oral and topical) and adrenalin eye drops was investigated with respect to the intraocular pressure. Healthy volunteers received different oral doses of propranolol, atenolol and timolol, and at the same time adrenalin eye drops in one eye. Healthy volunteers and patients with glaucoma received topical timolol and adrenalin. The investigations were randomised double-blind, except for the trial with glaucoma patients. The results showed that the effect on intraocular pressure of combining a beta-receptor-blocker and adrenalin can be either additive or antagonistic. The net result seems to depend on the degree of beta-blockade, being antagonistic with a strong beta-blockade and additive with a weak beta-blockade. The additive effect is present with both unselective and selective blockers. The effect seems to be independent of the mode of administration, oral or topical. A dose-response effect on intraocular pressure is seen with oral timolol although there is very little additional effect with doses greater than 5 mg. Beta-receptor blockers, both oral and topical, combined with adrenalin had an additive dilatating effect on the pupil size. The beta-receptor blockers also had a slight depressant effect on blood pressure and pulse rate.			
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Supplementum 150

From the Department of Ophthalmology
Hospital of Köping and Malmö General Hospital
University of Lund, Malmö, Sweden.

ADRENERGIC BETA-RECEPTOR BLOCKERS,
ADRENALIN AND INTRAOCULAR PRESSURE

by

Arne Öhrström



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"The time has come" the Walrus said
"To talk of many things:
Of shoes - and ships - and sealing wax -
Of cabbages - and kings -
And why the sea is boiling hot -
And whether pigs have wings".

Through the looking glass

L. Carrol 1872

This thesis is based on the following publications, referred to in the text by their Roman numerals:

- I Öhrström A and Pandolfi M
Hypotensive synergism of propranolol and adrenalin.
Ophthalmologica 179: 115-118 (1979)

- II Öhrström A and Pandolfi M
Regulation of intraocular pressure and pupil size by beta-blockers and epinephrine.
Arch. Ophthalmol. 98: 2182-2184 (1980)

- III Öhrström A and Kättström Ö
Interaction of timolol and adrenalin.
Brit. J. Ophthal. 65: 53-55 (1981)

- IV Öhrström A
Dose-related interaction between timolol and adrenalin.
Albrecht v. Graefes Arch. Klin. Ophthalmol. 216: 55-59 (1981)

- V Öhrström A
Dose-response of oral timolol combined with adrenalin.
In press. Brit. J. Ophthal.

CONTENTS

INTRODUCTION.....	7
MATERIAL AND METHODS.....	12
Definition of subjects.....	12
Drugs.....	13
Intraocular pressure.....	14
Pupil size.....	14
Pulse rate and blood pressure.....	14
Drug administration.....	14
Time of pre-treatment and treatment.....	15
Time of recording.....	19
Wash-out time.....	19
Design.....	19
Statistics.....	19
RESULTS.....	20
Side effects.....	20
Effects on IOP of systemic propranolol combined with adrenalin (I;II ₁).....	20
Effects on IOP of systemic atenolol combined with adrenalin (II ₁).....	22
Effects on IOP of systemic timolol combined with adrenalin (IV;V).....	22
Topical timolol combined with adrenalin	
1. Effects on IOP in healthy volunteers (II ₂).....	28
2. Effects on IOP in patients with open angle glaucoma and with exfoliation glaucoma (III)...	28

Relationship of time and IOP.....	30
Effects on pupil size (II;III).....	30
Effects on blood pressure and pulse rate (II).....	31
DISCUSSION.....	32
Degree of beta-blockade and effect of the association	
beta-blockers-adrenalin.....	33
Adaptation of the beta-receptors.....	34
Proposed mode of interaction adrenalin - beta-blockers.....	37
Weak or uncomplete beta-blockade.....	37
Strong or complete beta-blockade.....	38
Effects of adrenalin.....	39
Dose-response of beta-blockers on IOP.....	41
Pupil size.....	43
Effects on pulse rate and blood pressure (II).....	44
SUMMARY.....	45
ACKNOWLEDGEMENTS.....	46
REFERENCES.....	47

INTRODUCTION

The sympathetic part of the autonomic nervous system uses noradrenalin as the transmitter-substance at the nerve-effector junction. Adrenalin also stimulates the sympathetically innervated effectors. It is released from the adrenal medulla and enters the general circulation, thus also acting as a neuro-transmitter of the sympathetic system. At the effector site the two adrenergic transmitters (adrenalin and noradrenalin) stimulate the adrenergic receptors by binding to the site of the receptors on the target cell. (Fig.1).

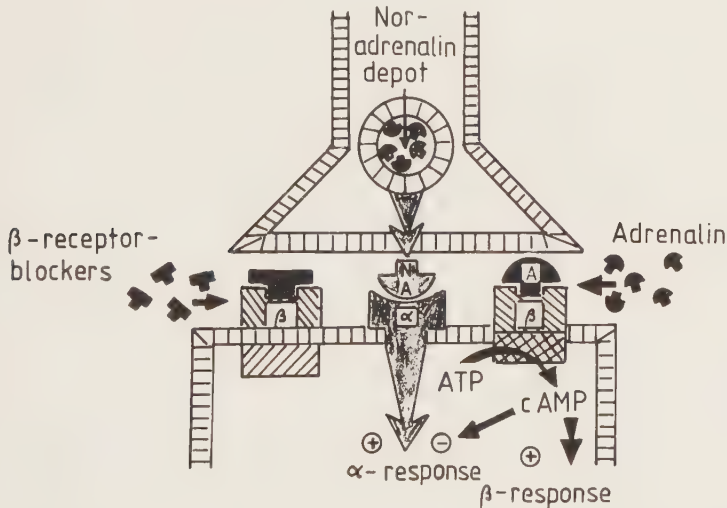


Fig. 1. Adrenergic neuromuscular junction: hypothetical action of a beta-receptor blocker to the left and to the right stimulation of a beta-receptor by adrenalin, which activates the enzymatic catalysis of cyclic AMP from ATP. In the middle, release of noradrenalin from a vesicle in the nerve terminal, which stimulates the alpha-receptor. adrenalin, A; noradrenalin, NA: alpha-adrenergic receptor, α ; beta-adrenergic receptor, β ; cyclic AMP, cAMP.
From A.H. Neufeld Survey of Ophthalmol. 1979 6/23 365.

The receptors have been classified as alpha and beta depending on their response to various sympathetic amines (1). The alpha-adrenergic receptor has a higher affinity for noradrenalin and phenylephrin, while the beta-adrenergic receptor is more sensitive for isoproterenol (2), a synthetic compound. Adrenalin stimulates both receptors.

Alpha-receptors usually have excitatory effects. resulting in smooth-muscle contraction in the sphincters of the gastro-intestinal tract and in blood vessels (vasoconstriction).

Beta-receptors usually mediate inhibitory effects (e.g. relaxation of smooth muscle) but can also be excitatory as for heart muscle contractility (3). The effects of the beta-receptors vary in different organs and thus the receptors are subdivided (4) into β_1 , mediating lipolysis and cardiac acceleration, and β_2 , mediating relaxation of smooth muscles, (as in broncho- and vaso-dilatation).

Stimulation of the beta-receptor, either by adrenalin or noradrenalin, activates adenylate cyclase, the enzyme that catalyzes the intracellular synthesis of cyclic AMP from ATP, and thus the concentration of cyclic AMP increases (2) (Fig.1). Cyclic AMP acts as a second-messenger intracellularly. The catalysis of cyclic AMP continues until the sympathetic amine (catecholamine) is inactivated by uptake into the surrounding cells. The amines can be inactivated both in the nerve terminal and in the post-junctional cell. Some of it can be re-used as a neuro-transmitter and stored in intracellular vesicles but major parts of the catecholamines are degraded by catechol-O-methyl transferase and mono-amine-oxidase (2).

If the receptor is occupied by a molecule which exerts no or little influence of it's own on the receptor, but blocks the receptor site for

the catecholamines, thus eliminating the possibility for an adrenergic receptor response, this molecule is a receptor-blocker. This blocking is exerted as a competitive inhibition, competitive with the catecholamines (Fig.1).

Alpha-receptor blockers, as thymoxamine and dibenamine, block specifically the alpha-receptor and have no influence on the beta-receptor.

The beta-receptors can also be blocked by specific substances which do not block the alpha-receptors. The first beta-receptor blocking drug was dichloroisoproterenol (5) but the first clinically useful one was propranolol, introduced by Black et al 1964 (6).

Beta-receptor blockers can be unselective, blocking both β_1 and β_2 , or selective, blocking one of the types of beta-receptor more than the other. Some beta-blockers while blocking the receptor site may also have a slight stimulating effect on the receptor, a property known as intrinsic sympathomimetic activity (ISA). (Table 1)

<u>Drug</u>	blocks		ISA
	β_1	β_2	
propranolol	+	+	0
alprenolol	+	+	+
practolol	+	0	+
pindolol	+	+	+
oxprenolol	+	+	+
metoprolol	+	0	0
timolol	+	+	0
atenolol	+	0	0

Table 1. Selectivity and intrinsic sympathomimetic activity, ISA, of some beta-adrenergic receptor blockers.

For an adrenergic receptor blocker to have an effect at the effector site, there must be a sympathetic tone (with consequent stimulation of the receptor) to be blocked. Without a sympathetic tone the blocker itself has no effect unless it has some intrinsic sympathetic activity. There is no known physiological beta-blocker and blocking of the receptors is a purely pharmacological inhibition of the adrenergic nervous system.

The above is a simplified review of the adrenergic receptors; in reality the situation is much more complicated. For instance, a number of studies have indicated that neither the number of receptors nor the ratio alpha to beta is stable. It has thus been shown that after prolonged treatment with adrenalin (7-10) there is a decrease in the number of beta-receptors, while after prolonged treatment with adrenergic beta-receptor blockers the number of beta-receptors increases (11). Furthermore, alpha-receptors can be changed into beta-receptors by exposure to cold or treatment with thyroid hormone (12-14).

Beta-adrenergic-receptor-blockers and intraocular pressure (IOP).

Beta-adrenergic receptors have been reported in structures of the eye involved in the regulation of the IOP (namely in the anterior segment and in the iris and ciliary body (15-17) of the rat eye), and evidence has been presented for an adrenergic innervation of the choroidal circulation, of the ciliary body and processes, and of the irido-corneal angle (18-21) of rats, rabbits and primates.

In the eye both beta-receptor agonists (22-25) and antagonists

(26-27) have been shown to lower the intraocular pressure. In 1970 Bill (28) showed that beta-adrenergic stimulation increased the production of aqueous humor and increased the facility of outflow, while in 1976 Takase (29) stated that both beta-agonists and antagonists reduced the production of aqueous humor.

The situation is further complicated by the fact that both alpha-stimulation and alpha-blockade (30-32) have been shown to have a hypotensive effect. However, most of these trials were done on animals and the findings cannot necessarily be extrapolated to humans.

The first report of a beta-blocker reducing IOP is that of Phillips (33), who in 1967 reported that propranolol lowered the intraocular pressure in patients with glaucoma and in subsequent studies almost every clinical available beta-blocker (Table 1), whether given topically or systemically, has been shown to have an IOP-lowering capacity (3;26;34).

The potential benefits of a new kind of drug in the treatment of glaucoma encouraged clinical trials with beta-blockers in glaucoma (26; 35-37). Used alone, either topically or systemically or in combinations with conventional glaucoma treatment beta-blockers have had an IOP-lowering effect (35; 38-43).

When the beta-blocker timolol was introduced as a drug for the treatment of glaucoma (44-46) reports confirmed the additional hypotensive effect of topical timolol and the usual glaucoma drugs, mainly pilocarpine and carbonic anhydrase inhibitors (38-39). However the combination of beta-blockers with topical adrenalin had not been fully investigated when this study started (1979). The combination of an adrenergic agonist, (adrenalin) with an adrenergic antagonist (beta-adrenergic -receptor blocker)

may seem paradoxical, and in fact clinical reports and other studies with these two drugs have reported conflicting results (35; 38-43; 46-47)

However, it was thought that the combination of adrenalin and a beta-blocker could possibly avoid the well-known side-effects of miotics and carbonic anhydrase inhibitors, while having a useful depressant effect on the intraocular pressure.

The present investigation was undertaken to elucidate the effects on IOP of beta-blockers combined with adrenalin.

MATERIAL AND METHODS

Definition of subjects

Studies I, II, IV and V were on healthy volunteers. 21 females (age-range 18 - 48 years; mean 35) and 6 males (age-range 22 - 45; mean 33) were studied. Many of them took part in all the studies.

In study I there were 4 men and 6 women; in the first part of study II 10 women and 2 men, and in the second 9 women and 1 man; in study IV 10 women; and in study V 12 women.

In study III patients with newly-detected untreated glaucoma were studied. Ten patients 4 women and 6 men with glaucoma simplex aged 54 - 82 (mean 71) and ten patients 7 women and 3 men with exfoliative glaucoma aged 46 - 86 (mean 72).

Informed consent was obtained from patients and volunteers according to the declaration of Tokyo-Helsinki.

The studies were approved by the Ethical Committëe of the Central Hospital, Västerås.

DRUGS

Oral propranolol. Study I and II.

Propranolol 40 mg, propranololhydrochloride (Inderal[®], ICI) was dispensed as capsules by the local pharmacy. Colouring with methylene blue was added.

Oral atenolol. Study II.

Atenolol 50 mg, atenolol hydrochloride (Tenormin[®], ICI) was dispensed as capsules in the same way as for propranolol.

Topical timolol. Study II and III.

0.5% timolol maleate (Blocadren[®], MSD) ophthalmic solution was used and dispensed into new "blind" bottles identical for placebo.

Oral timolol. Study IV and V.

Timolol maleate (Blocadren[®], MSD) was dispensed as capsules by the local pharmacy in different doses ranging from 2.5 mg to 15 mg per capsule and coloured with methylene blue.

Topical Adrenalin.

2% adrenalin hydrochloride (Glaufirin[®], Allergan) was used in study I and II. 1% adrenalin borate (Eppy[®], Pharmacia) was used in the second part of II and in III, IV and V. Adrenalin and placebo drops were dispensed in identical "blind" bottles.

Placebo.

Capsules identical to those containing active substance were filled with lactose and slightly coloured with methylene blue. They were used in studies I, II, IV and V.

As placebo eyedrops 0.15 M NaCl solution was used.

METHODS

Intraocular pressure.

The intraocular pressure was measured with a Goldmann applanation tonometer, calibrated daily. 1-2 drops of 0.25% sodium fluorescein with 0.4% oxibuprocain hydrochloride were used for staining and anaesthesia (Fluress[®], Pharmacia).

Pupil size.

The horizontal pupillary diameter was determined with the pupillometer of a Goldmann projection perimeter in standard conditions of luminance.

Pulse rate and blood pressure.

After the subject had rested for 5 min. in a chair, blood pressure was determined with a mercury sphygmomanometer and pulse rate measured.

Drug administration.

Studies I, II, IV and V.

Placebo and active substance were administered in a randomised double-blind cross-over fashion. All the subjects had to take care of their

drug administration themselves and no one reported any difficulties in taking the drugs. For each individual subject the adrenalin was instilled in the same eye throughout the trial with placebo drops in the other. The distribution between left and right eyes was randomised but balanced, so that the same number of left and right eyes were treated with the active substance.

Study III

In study III the treatment with timolol drops was not coded but the treatment with adrenalin or placebo was randomised and double-blind. The patients instilled the timolol drops themselves during the two weeks of pre-treatment at home, while after admission to the hospital treatment was handled by a special nurse.

Half of the patients received adrenalin and half placebo. There was no cross-over. The differences in tension in each eye were analysed by using the values from the first two days with timolol only and comparing them with those from the next two days after the addition of the randomised coded treatment.

Time of pre-treatment and treatment.

In order to achieve a steady state in the pharmaco-kinetics of the oral drug pre-treatment was started before the recordings in all the studies except study II₂, which was a single dose study (Table 2). A pre-treatment period of at least 4 times the half-life of the drug was considered necessary (48).

Drugs	I SYSTEMIC propranolol + adrenalin	II ₁ SYSTEMIC propranolol and atenolol + adrenalin	II ₂ LOCAL topical timolol + adrenalin
Design	Randomized double-blind crossover	Randomized double-blind crossover	Randomized double-blind crossover
Time of the trial Includ. wash out time	2 weeks	3 weeks	2 weeks
Recording days	3 days x 2	2 days x 3	3 days x 2
Time of tonometry	9.00, 12.30, 16.00.	9.00,10.30,12.00, 13.30,15.00, 16.00.	9.00,11.20,13.40, 16.00.
Pre-treatment time	2 days	None	12 hours
Wash out time	4 days	5 days	10 days
Number of subjects	10 healthy volunteers	12 healthy volunteers	10 healthy volunteers
Dose and time for dosage	Propranolol 40 mg x 2, 7.00 and 14.00 Adrenalin 2% x 2 8.00 and 15.00	Propranolol 40 mg x 1. 6.00 Atenolol 50 mg x 1 6.00 Adrenalin 2% x 1 8.00	Topical timolol 0.5% x 2, 7.00 and 19.00 Adrenalin 1% x 2 8.00 and 13.00

Table 2
Design of the trial
drugs, subjects, dosages and time table

III LOCAL	IV SYSTEMIC	V SYSTEMIC
topical timolol + adrenalin	oral timolol + adrenalin	oral timolol + adrenalin
Randomized double- blind	Randomized double- blind crossover	Randomized double- blind crossover
4 days	4 weeks	6 weeks
2 days control 2 days treatment	3 days x 2	2 days x 6
8.00, 12.00 16.00.	8.00,10.00,12.00 14.00,16.00.	8.00,10.00,12.00, 14.00,16.00.
2-3 weeks	4 days	12 hours
—	14 days	5 days
10 glaucoma simpl. patients 10 glaucoma exfol. patients	20 healthy volunteers	12 healthy volunteers
Topical timolol 0.5% x 2, 7.00 and 19.00. Adrenalin 1% x 2 7.15 and 19.15.	Oral timolol x 2 2.5 mg and 10 mg 7.00 and 19.00. Adrenalin 1% 7.00 and 13.00.	Oral timolol x 2 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg. 7.00 and 19.00. Adrenalin 1% 7.00 and 13.00.

As the half-life of propranolol (49) is about 4.3 hours and of oral timolol between 2-5 hours (50), these requirements were fulfilled in studies I, III, IV and V.

The half-life of topical timolol is not known, but 5-46% is excreted in the urine during 24 hours (51). However, this elimination coefficient is of doubtful accuracy as the plasmaconcentration were frequently below detection limit in that study (51). In study II₂ with topical timolol in healthy volunteers, a pre-treatment time of 12 hours was thus considered sufficient.

No pre-treatment was given with adrenalin because of the very short half-life for this drug.

Statistical analysis revealed no differences between the recording days in the different trials that could be ascribed to a possible non-steady state. The pre-treatment was started at the same time of day as the treatment was given on the recording days.

The treatment times are shown in table 2. As can be seen, the temporal relationship between the administration of the beta-blocker and the adrenalin varies between the different studies. For example, in study I propranolol was given at 07.00 and 14.00 with adrenalin on each occasion. 1 hour later (at 08.00 and 15.00), whereas in study V timolol was given at 07.00 and 19.00 with adrenalin at 07.00 and 13.00. (See table 2 for further details).

Time of recordings.

The first IOP recording was made 1 hour after the instillation of adrenalin, except in study III where the interval was 45 min. The recording interval varied between 1 1/2 hour and 4 hours (Table 2).

Wash-out time.

To eliminate carry-over effect from the previous drug the wash-out time was calculated with respect to the half-life of the drug.

Half-life propranolol 4.33 hours (49)

" atenolol 6-7 hours (52)

" timolol 2-5 hours (50)

" topical timolol (51), not known, but 5-46% is excreted in the urine during 24 hours.

As shown in table 2, the wash-out times for propranolol were 4 and 5 days, respectively, (I and II); for oral timolol (in studies IV and V) 5 and 14 days, respectively; and for topical timolol 10 days (II₂).

Design.

The designs of the studies are shown in table 2.

Statistics.

The number of patients was selected to be that most suitable for an analysis of variance, and the drug administration was randomised, double-blind cross-over, in order to eliminate possible bias. However, in study III the cross-over had to be omitted of practical reasons. The results were analysed by Fisher's test (analysis of variance quotient) and by the non-parametric Kendall rank correlation test.

RESULTS

Side effects.

While on placebo one of the subjects had an attack of renal colic secondary to a stone and could not complete the trial (IV). In study V one of the subjects developed bradycardia (45 beats/min) and had to leave the study. Her dose of timolol was 10 mg a day. The only other side effects were minor ones, e.g. slight stinging in the eyes.

Effects on IOP of systemic propranolol combined with adrenalin (I;II).

In study I oral propranolol 40 mg was given twice a day and 2% adrenalin hydrochloride twice a day and in study II a single dose of propranolol 40 mg was combined with a single dose of topical 2% adrenalin hydrochloride. Both studies showed a significant hypotensive effect of propranolol or adrenalin alone ($p < 0.01-0.001$) (Table 3 and 4). A synergistic additive hypotensive effect of the combination propranolol-adrenalin was demonstrated in both trials ($p < 0.001$) fig. 2 and 3, the decrease caused by propranolol being larger than that produced by adrenalin ($p < 0.001$).

Placebo 14.157 ± 0.1616 (90)	Placebo + adrenalin 13.222 ± 0.1616 (90)
Propranolol 12.111 ± 0.1616 (90)	Propranolol + adrenalin 11.378 ± 0.1616 (90)

Table 3 (study I) Mean IOP during the last 3 days of the study. Figures in brackets denote number of measurements. Mean $\pm$ SD mm Hg.

	Placebo, Oral	Propranolol, Oral	Atenolol, Oral
Placebo drops	13.833 $\pm$ 0.141	12.639 $\pm$ 0.140	11.486 $\pm$ 0.139
Adrenalin drops	12.778 $\pm$ 0.141	12.097 $\pm$ 0.140	11.042 $\pm$ 0.139

Table 4 (study II₂). Intraocular pressure during treatment. Mean IOP $\pm$ SEM mm Hg derived from the pooled variance estimate in the analysis of variance.

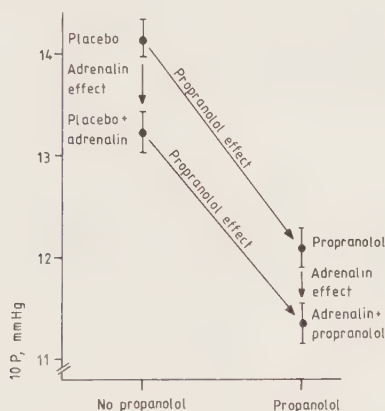


Fig. 2. IOP-lowering effect of adrenalin or propranolol alone or both substances combined. For explanations see text.

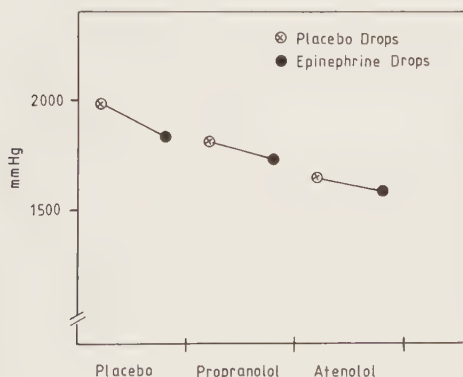


Fig.3. Sum of 144 intraocular pressure measurements (ordinate) in three groups of patients receiving topical adrenalin or placebo and various kinds of oral treatment (abscissa). (Epinephrine = adrenalin)

Effects on IOP of systemic atenolol combined with adrenalin (Study II).

A single dose of atenolol 50 mg was combined with a single dose of 2% adrenalin hydrochloride. Both atenolol and adrenalin alone lowered the IOP significantly ($p < 0.001$) (table 4). The drugs combined had an additive hypotensive effect, which was greater than either drug used alone ($p < 0.001$). The atenolol-adrenalin effect was significantly greater than the effect of adrenalin combined with 40 mg propranolol ($p < 0.001$). (Table 4 and fig. 3).

Effects on IOP of systemic timolol combined with adrenalin (Study IV,V).

In study IV oral timolol was combined with 1% adrenalin borate. Timolol was given in doses of either 2.5 mg x 2 or 10 mg x 2 daily. The analysis (table 5) showed a highly significant ($p < 0.001$) effect of oral timolol 2.5 mg and of adrenalin when each drug was given alone, but the adrenalin-timolol combination did not have a significant effect.

	Mean IOP $\pm$ SEM	n	Mean reduction $\pm$ SEM
Placebo/placebo	12.874 $\pm$ 0.334	150	
Placebo/adrenalin	11.941 $\pm$ 0.334	150	0.9333 $\pm$ 0.4722
Timolol/placebo	11.474 $\pm$ 0.334	150	1.4000 $\pm$ 0.4722

Table 5. Mean IOP during the trial with 2.5 mg timolol twice a day, including all subjects and with no correction for timolol-insensitive subjects.

Due to highly significant individual differences in IOP responses, the mean total differences of the single subjects between the week with timolol and the week with placebo were analysed, which showed three non-responders to timolol. Accordingly, the analysis was corrected, and the recordings of the three non-responders were excluded. This left six subjects, of whom four took placebo capsules during week 1 and timolol during week 2, while two took timolol during the first week and placebo during the second. The new analysis of variance was based on 360 recordings of IOP (table 6).

	Mean IOP $\pm$ SEM	n	Mean reduction $\pm$ SEM
Placebo/placebo	13.07 $\pm$ 0.3137	90	
Placebo/adrenalin	11.98 $\pm$ 0.3137	90	1.0889 $\pm$ 0.4436
Timolol/placebo	11.08 $\pm$ 0.3137	90	1.9889 $\pm$ 0.4436
Timolol/adrenalin	10.39 $\pm$ 0.3137	90	2.6778 $\pm$ 0.4436

Table 6. Mean IOP during the trial with 2.5 mg timolol twice a day. Results from six subjects, the timolol-insensitive subjects having been excluded.

The analysis showed that timolol caused a highly significant ($p < 0.001$) reduction of IOP. Adrenalin used alone reduced the IOP less ($p < 0.05$). The drugs combined reduced the IOP more than either drug alone. According to the analysis of variance there was no significant interaction and thus an additive effect was most likely. Though this analysis was corrected for timolol-insensitive subjects the individual IOP responses were still significantly heterogenic ($p < 0.01$).

	Mean IOP $\pm$ SEM	n	Mean reduction $\pm$ SEM
Placebo/placebo	13.920 $\pm$ 0.122	150	
Placebo/adrenalin	13.520 $\pm$ 0.122	150	0.400 $\pm$ 0.173
Timolol/placebo	11.413 $\pm$ 0.122	150	2.507 $\pm$ 0.173
Timolol/adrenalin	12.000 $\pm$ 0.122	150	1.920 $\pm$ 0.173

Table 7. Mean IOP during the trial with 10 mg timolol twice a day.

As shown in table 7 the hypotensive effect of timolol capsules (10 mg x 2 daily) was highly significant ($p < 0.001$) and was more effective than adrenalin alone. Adrenalin combined with placebo capsules showed a small but significant ($p < 0.05$) reduction of IOP. Adrenalin combined with timolol had an antagonistic effect, as the combination was not as effective as timolol-placebo. The difference was highly significant ($p < 0.001$). The individual responses to the treatment were highly significant ($p < 0.001$) but the day, the time of recording, or whether it was the first or second period of treatment had no significant effect on the results.

Study V.

In study V different doses were used (2.5, 5, 7.5, 10 and 15 mg, all twice daily). The hypotensive effect of oral timolol alone was confirmed ($p < 0.001$). The study showed that with a small dose of timolol (5 mg - 10 mg daily) the effect with adrenalin was additive, while with larger doses (10 mg - 30 mg daily) the effect was antagonistic (Fig. 4).

When the differences in IOP values were formed between adrenalin and placebo treated eyes at the five dose levels of timolol, ($\Delta E-P$), a linear correlation of the means emerged (table 8 fig. 5), which is suggestive of a gradual inhibition of the adrenalin effect with increasing timolol dose. The analysis of this correlation using the mean IOP differences was of highest significance ($p < 0.001$) using parametric statistics, and of high significance ($p < 0.0083$) in the non-parametric Kendall rank correlation test.

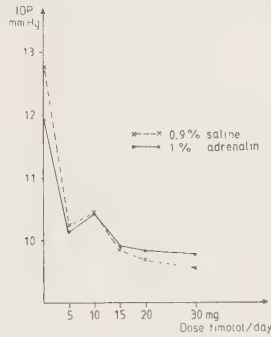


Fig. 4. Dose-response curve of oral timolol with 0.9% saline drops in one eye and 1% adrenalin in the other eye. Every point represent the mean of 110 recordings.

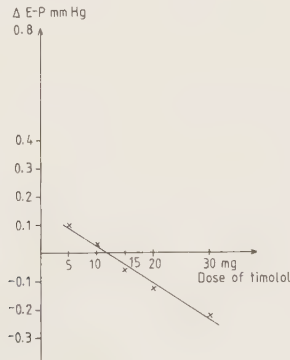


Fig. 5. $\Delta E-P$ show the differences in intraocular pressures between the eye treated with adrenalin and the eye treated with 0.9% saline with different oral doses of timolol.

Oral dose	Topical treatment		n	Δ E-P
	Adrenalin drops	Placebo drops		
Placebo	11.918 $\pm$ 0.1661 p < 0.001	12.764 $\pm$ 0.1661 p < 0.001	2 x 110	- 0.845
5 mg	10.127 $\pm$ 0.172	10.227 $\pm$ 0.172	2 x 110	- 0.100
10 mg	10.409 $\pm$ 0.161	10.436 $\pm$ 0.161	2 x 110	- 0.0273
15 mg	9.9000 $\pm$ 0.1545	9.836 $\pm$ 0.1545	2 x 110	0.0636
20 mg	9.918 $\pm$ 0.1510	9.691 $\pm$ 0.1510	2 x 110	0.1273
30 mg	9.773 $\pm$ 0.1415	9.546 $\pm$ 0.1415	2 x 110	0.2277

Table 8. Mean intraocular pressure $\pm$ SEM mm Hg with different doses of timolol. 0.9% saline in one eye and 1% adrenalin in the other. Δ E-P decrease of intraocular tension following adrenalin drops. Each figure represents the mean of 110 recordings.

In the full analysis of variance, including both eyes treated with placebo drops and adrenalin, the contrasts between "eyes" (reaction of IOP) and between timolol doses were statistically non-significant, showing no further lowering of the IOP with increasing timolol doses. However, when the half of the readings in study V (table 9) in which no adrenalin was applied was analysed (table 10), an increase in timolol dose was followed by a decrease in IOP values ($p < 0.05$), which is suggestive of a tendency to a dose-response relationship.

Dose: mg	5	10	15	20	30	
Individual	IOP Totals					Sum
No 1	100	97	98	99	95	489
2	114	111	95	96	120	536
3	94	84	81	81	66	406
4	85	96	117	126	102	526
5	120	119	110	119	121	589
6	87	86	81	72	79	405
7	94	105	94	89	93	475
8	91	93	93	83	82	442
9	93	87	83	78	79	420
10	129	137	112	119	107	604
11	118	133	118	104	106	579
Sum	1125	1148	1082	1066	1050	5471=Grand total

Table 9. Timolol treatment without adrenalin. Sum of recordings of IOP during day I and II (IOP totals) at different dose levels of timolol. Measurements in mm Hg.

Analysis of variance	Sum of squares	d.f.	Mean Square	F	P
Between individuals	11048.91	10	1104.89	13.99	<.001
Linear between doses	468.59	1	468.59	5.94	<.05 (<0.02)
Non-linear " "	144.21	3	48.07	<1	n.s.
Exp. error	3158.00	40	78.95 = s_0^2		
Total	14819.71	54			

Table 10. Analysis of variance of the IOP totals at different dose levels of timolol obtained in table 9. d.f. = degrees of freedom. F = Fisher's variance quotient.

The hypotensive effect of pure adrenalin was weak but significant ($p < 0.05$) in study IV. In study V the adrenalin effect alone was not significant. However, a closer analysis revealed an individual who reacted with an increase of IOP after adrenalin. If this particular subject had been excluded, adrenalin would have shown a highly significant hypotensive effect. However, in order not to disturb the validity of the statistical analysis no values were excluded and the tables thus includes this inverse reaction.

TOPICAL TIMOLOL COMBINED WITH ADRENALIN (STUDIES II₂ AND III)

Effects on IOP in healthy volunteers. Study II₂.

0.5% timolol eye drops were given twice daily 07.00 and 19.00, and 1% adrenalin twice daily 08.00 and 13.00. Timolol or adrenalin alone showed a highly significant hypotensive effect ($p < 0.001$). (Table 11). Timolol combined with adrenalin lowered the IOP less than timolol alone ($p < 0.001$) indicating an antagonism. This antagonism resulted in the total effect of adrenalin in the analysis of variance being virtually nil.

	Placebo drops	Timolol drops
Placebo drops	14.440 $\pm$ 0.144	11.550 $\pm$ 0.144
Adrenalin drops	13.700 $\pm$ 0.144	12.283 $\pm$ 0.144

Table 11. Intraocular pressure during treatment. Measurements in mm Hg. Mean $\pm$ SEM derived from the pooled variance estimate in the analysis of variance.

Effects on IOP in patients with open angle glaucoma (simplex) and with exfoliation glaucoma. Study III.

10 patients of each category were pre-treated with 0.5% topical timolol for at least two weeks. After admission to hospital 1% adrenalin or placebo was added on the third and fourth days after admission. In both groups adrenalin showed a highly significant ($p < 0.01 - 0.001$) additive hypotensive effect. The effect being most pronounced in the exfoliative group ($p < 0.001$). In both groups the patients randomised to placebo showed an increase of IOP, which is impossible to explain. (Table 12 and 13).

Glaucoma simplex. 10 patients.					
Day 1 + 2			Day 3 + 4		
Placebo	20.875 $\pm$ 3.280	n = 72 (9 eyes)	Adrenalin	19.875 $\pm$ 3.680	
Placebo	19.50 $\pm$ 3.871	n = 72 (9 eyes)	Placebo	20.875 $\pm$ 4.838	
=====					
Exfoliation glaucoma. 10 patients.					
Day 1 + 2			Day 3 + 4		
Placebo	23.875 $\pm$ 14.700	n = 48 (6 eyes)	Adrenalin	17.833 $\pm$ 6.501	
Placebo	25.812 $\pm$ 12.084	n = 64 (8 eyes)	Placebo	27.937 $\pm$ 12.031	

Table 12. Mean values of intraocular pressure (mm Hg $\pm$ SD) on days 1 + 2 (control period) and on days 3 + 4 (treatment period).
n = number of recordings.

	Glaucoma simplex. 10 patients.	Exfoliation glaucoma. 10 patients.
	Mean reduction $\pm$ SEM	Mean reduction $\pm$ SEM
Adrenalin	- 1.00 $\pm$ 0.346 (9 eyes)	- 6.042 $\pm$ 0.577 (6 eyes)
Placebo	+ 1.375 $\pm$ 0.346 (9 eyes)	+ 2.125 $\pm$ 0.4997 (8 eyes)

Table 13. Mean reduction of intraocular pressure (mm Hg) during the 2 days of combined treatment (days 3+4) compared to the control period (days 1 + 2).

Relationship of time and IOP.

The statistical analysis showed a declining effect on IOP during the day in the single dose trial, II₁, which is not surprising. In the other trials there were no significant differences related to the time or day of measurement.

Effects on pupil size. Studies (II + III).

Study II₁.

2% adrenalin combined with oral propranolol 40 mg or atenolol 50 mg increased the pupil size more than adrenalin alone ($p < 0.01$). Oral propranolol alone did not change the pupil size significantly, while oral atenolol slightly increased the pupil size ($p < 0.001$). Table 14. The differences in pupil size between placebo and placebo plus adrenalin was not significant.

II ₁	Placebo drops	Adrenalin drops
Placebo oral	3.8819 $\pm$ 0.0370	3.8125 $\pm$ 0.0344
Propranolol oral	3.8125 $\pm$ 0.0324	3.9514 $\pm$ 0.0325
Atenolol oral	3.9722 $\pm$ 0.0380	4.0347 $\pm$ 0.0365

II ₂		
Placebo drops	3.8667 $\pm$ 0.084 **	4.0167 $\pm$ 0.084 **
Timolol drops	3.9167 $\pm$ 0.084 **	4.100 $\pm$ 0.084 **

Table 14. Pupil size* during treatment in study II₁ and II₂.

* Measurements in millimeters, mean $\pm$ SEM.

** The SEM derived from the pooled variance estimate in the analysis of variance.

Study II₂.

Topical timolol or adrenalin alone did not induce any significant changes in pupil size. However, the combination of timolol and adrenalin produced a slight but significant increase in pupil size ($P < 0.05$) (Table 14).

Study III.

In study III, because of the pre-treatment period with timolol, it was not possible to analyse the effect of timolol on the pupil, but after the addition of 1% adrenalin there was a highly significant ($p < 0.001$) dilatation of the pupil.

No significant effect was observed with placebo.

Effects on blood pressure and pulse rate. Study II.

A lowering of the pulse rate was observed ($p < 0.001$) during treatment with oral propranolol 40 mg and oral atenolol 50 mg. The systolic blood pressure also showed a significant decrease during these treatments ($p < 0.001$). In neither case was there any significant difference between the two beta-blockers. Topical timolol 0.5% reduced the pulse rate slightly ($p < 0.01$) and slight reduction of the systolic blood pressure was also observed ($p < 0.05$). Table 15.

	Blood pressure mm Hg	Pulse rate, beats per minute
Placebo oral	118.4 $\pm$ 0.976	75.00 $\pm$ 0.75
Propranolol oral	113.4 $\pm$ 0.976	64.58 $\pm$ 0.75
Atenolol oral	112.7 $\pm$ 0.976	63.33 $\pm$ 0.75
Placebo drops	113.67 $\pm$ 0.58	79.2 $\pm$ 0.746
Timolol drops	111.92 $\pm$ 0.58	76.13 $\pm$ 0.746

Table 15. Pulse rate and blood pressure (systolic) during treatment with beta-blockers in study II₁ and II₂. (Mean $\pm$ SEM).

DISCUSSION

Both oral and topical beta-blockers have been compared with the usual anti-glaucoma treatment (53-60). The results have generally shown an equal or superior hypotensive effect of the beta-blockers. Adrenergic beta-receptor blockers have been tried with miotics and with carbonic anhydrase inhibitors and the combinations have had an additive hypotensive effect (53-55). The combination of a beta-blocker and an unselective adrenergic drug such as adrenalin seems paradoxical and until recently only a few reports on the combination of topical beta-blockers with adrenalin had been published (61-66).

Tregubova (67) demonstrated an additive hypotensive effect of topical 1% propranolol and 2% adrenalin in patients with open angle glaucoma simplex. Favourable results with topical timolol and adrenalin, showing an additive IOP-reducing effect have also been reported (39;40;56;64;68). Higgins and Brubaker (63) found that this combination was additive on inhibiting the formation of aqueous humor, but found no significant decrease in the IOP. However, Schenker et al (68) found a significant decrease of the IOP after combining topical timolol and adrenalin. Topical atenolol combined with adrenalin was shown by Rushton (66) to have an additive hypotensive effect.

On the other hand, Phillips (61) reported that the combination of local atenolol and adrenalin was less effective than atenolol alone and Boger et al (42) could not find any additive hypotensive effect of adrenalin in patients already receiving timolol drops. Goldberg (62) reported that prior treatment with topical timolol for a week

significantly diminished the IOP-reduction produced by adrenalin.

The present studies II₂ and III with topical timolol and adrenalin showed both antagonistic and additive effects.

The interaction of oral beta-blockers and adrenalin has been investigated even less than that of topical beta-blockers and adrenalin. Only open clinical reports (including all possible glaucoma drugs) have suggested additive effects of oral propranolol and adrenalin (35;47).

The present studies demonstrate that both oral propranolol (I and II₁) and oral atenolol (II₁) potentiate the hypotensive effect of adrenalin. Oral timolol (IV and V) in low doses also has an additive effect when combined with adrenalin, but in higher doses (10 - 30 mg daily) the reaction is antagonistic. The hypotensive effect of adrenalin diminishes linearly as the timolol dose is increased, which finally makes the combination less effective than timolol alone. Thus the combining of beta-blockers with adrenalin has given conflicting results.

Degree of beta-blockade and effect of the association beta-blockers - adrenalin.

Bonomi (34) compared the hypotensive effect of 8 different beta-blockers given topically but could not find any certain correlation between the usual beta-blocker potency measured systemically (69) and the intraocular hypotensive effect when given topically. Unfortunately there is no dose-response study comparing the effects on IOP of different beta-blockers given orally. A comparison of the beta-blocker potency ratio, based on the inhibition of isoprenaline-induced

tachycardia (69), has shown timolol to be six times more potent than propranolol and atenolol. Thus the oral doses used with propranolol and atenolol in study I and II are largely comparable to a low dose of oral timolol. As beta-blockers act by competitive inhibition a high oral dose should provide a greater degree of beta-blockade than a low dose. With a low dose of timolol or the doses of propranolol and atenolol used the systemic beta-blockade can be assumed to be weak and the effects of combination with adrenalin have been additive. With a larger dose of timolol the beta-blockade is more complete and the combination with adrenalin gives an antagonistic effect. These results suggest that the factor that determines antagonism or agonism is the varying degree of beta-blockade.

Adaption of the beta-receptors.

In study II₂ with healthy volunteers the combination of topical timolol and adrenalin was antagonistic, while in study III with glaucoma patients the combination had an additive effect.

Although there are many difficulties in comparing the two clinical trials II₂ and III, the main differences between the studies were the intervals between the adrenalin dosages and the pre-treatment times. However, the time interval of 5 hours between the adrenalin dosages in II₂ was the same as in study IV and V, in which both additive and antagonistic effects were demonstrated. This suggests that it is not the interval between adrenalin administrations which is important in determining between antagonistic and additive effects. In both groups 0.5% timolol ophthalmic solution was instilled twice daily (07.00 and

19.00). The patients received 1% adrenalin a quarter of an hour after each timolol dose (07.15 and 19.15) but the volunteers were given it at 08.00 and 13.00. The pre-treatment time was 12 hours for the volunteers and at least 2 weeks for the patients.

Thomas and Epstein (64) studied the combined effects of topical timolol and adrenalin on glaucoma patients but with a pre-treatment period for each of the drugs of 2 weeks. They found an additive effect of the combination that was most marked after pre-treatment with adrenalin. However, after treating for 8 weeks with both drugs, no significant additive effect was found.

Schenker et al (68) also investigated the effects of topical timolol and adrenalin each drug alone and then the combination and had similar results although the decrease in IOP was not significant when adrenalin was added after pre-treatment with timolol.

Other reports of long-term treatment with timolol (70-73) report a slowly diminishing effect, which suggest an adaption of the beta-receptors during prolonged blocking. Neufeld et al (11) showed in rabbits that topical treatment with timolol for 4 days caused an increase in the density of the beta-receptors in the eye. Other investigators (7-10) have shown a decrease of the beta-receptor population during prolonged beta-adrenergic stimulation in other organs of the body.

Probably this change of the beta-receptor population, increasing with blockade and decreasing with stimulation, may be responsible for the long term reduction of effect of both beta-blockers and adrenalin.

In study III, which deals with glaucoma patients, the prolonged pre-treatment time probably caused an adaption and an increase of the

beta-receptor population, resulting in weaker beta-blockade than at the beginning of the treatment.

This change in the degree of beta-blockade may explain the different results between the studies II₂ and III with topical timolol. In study II₂ the beta-receptors did not manage to adapt themselves to the blocking agent and thus the beta-blockade was more efficient than in study III, in which the longer adaption time led to a less efficient blockade.

Thus a possible conclusion is that adrenalin combined with an efficient beta-blockade has an antagonistic effect.

This is similar to the results of oral beta-blockers combined with adrenalin, where a high dose of the beta-blocker, producing an efficient blockade was antagonistic, while a low dose, producing an inefficient blocking, was additive in lowering the IOP.

Another theoretical explanation for the differences in effect shown for topical timolol (i.e. agonism and antagonism) would be that there is a difference in its modes of action in glaucoma eyes and healthy eyes.

This does not seem very plausible as both timolol and adrenalin alone reduce the IOP in both patients (62;64) and volunteers (44;74)

It could be that the IOP-reducing mechanism is different depending on whether the beta-blocker is administrated topically or orally. However, this also seems unlikely as most beta-blockers tested lower the IOP with either mode of administration (26;34)

Proposed mode of interaction adrenalin - beta-blockers.

The observations in this paper of an additive effect with adrenalin of a low oral beta-blocker dose and an antagonistic effect of a high oral dose, and that with an increasing beta-blocker dose the effect of adrenalin decreases, may possibly be explained by consideration of the following points:

1. The reduction of IOP by topical timolol has been shown by fluorophotometry (75-76) to be due to a decreased formation of aqueous humor.
2. In another fluorophotometric study of adrenalin (74) the immediate IOP-reducing effect of adrenalin resulted from an increase in the facility of outflow which exceeded a concomitant increase in the production of aqueous humor.
3. In a comparison between timolol and adrenalin the IOP-reducing effect of topical timolol was significantly greater than that of adrenalin (41).
4. There seems to be no reason to believe that the basic mechanism producing the reduction of IOP differs between oral and topical timolol, and thus oral timolol also probably reduces the formation of aqueous humor.

Weak or uncomplete beta-blockade.

With a weak beta-blockade there are still beta-adrenergic receptors in the eye susceptible to stimulation by adrenalin. (Fig.1). Adrenalin is thus still capable of increasing the facility of outflow and this effect is still greater than the effect on the stimulation of the production of aqueous humor, and consequently the net effect will be a further reduction of the IOP.

Strong or complete beta-blockade.

If the adrenergic effect on the facility of outflow is dependent on beta-receptors it would be possible to block this effect. Thomas and Epstein (64) found with tonography that timolol blocked the adrenalin effect on the facility of outflow, which may indicate that beta-receptors are involved in the regulation of the facility of outflow. However, the beta-blocker itself has been shown to have practically no effect of its own at the chamber angle (75-76). This absence of effect would be possible to explain if the normal beta-adrenergic tone regulating the facility of outflow is very low or the receptors are sparse. That assumption is corroborated by Ehinger (30), who has shown that in primates the adrenergic innervation in the trabecular mesh-work is sparse, but more abundant in the ciliary body.

With a complete beta-blockade there would be very few beta-receptors concerned with the outflow susceptible to stimulation by adrenalin, and the increase in the facility of outflow mediated by adrenalin would thus be negligible.

In the ciliary body beta-receptor blockade decreases the production of aqueous humor, while adrenalin stimulates the beta-receptors to increase the production of aqueous humor.

The addition of adrenalin to receptors being completely blocked with a competitive beta-receptor blocker must lessen the inhibition of the beta-receptor function, thus making the beta-blockade less effective than if the blocker were used alone.

The expression "complete blockade" is used, but of course there is never complete blockade with a competitive inhibition of the

receptors, only varying degrees of blockade. "Complete" is thus synonymous with a high degree of blockade.

Effects of adrenalin.

The hypotensive action of adrenalin has been demonstrated in all studies I - V. The effect has been comparatively small but probably this is due to the choice of healthy volunteers as subjects, (except in study III, when glaucoma patients were studied) as it is more difficult to lower a already normal IOP than a higher pathological one (77). Usually the mean base-line IOP was around 13 mm Hg, thus after a reduction of 2-3 mm Hg the IOP would be only slightly higher than the episcleral venous pressure and a further decrease below the episcleral venous pressure is not really to be expected.

Paradoxical increase of IOP.

One subject in study V demonstrated an increase of tension after adrenalin. This phenomenon has been reported before (78), with the suggestion that the hypertensive effect of adrenalin is due primarily to intraocular vascular responses that increase the episcleral venous pressure. This paradoxical reaction was also studied in cats by Rowland and Potter (25), when it was shown to be due to a contraction of the extraocular muscles.

Maximal adrenergic stimulation.

One of the objectives during this investigation was to maintain a maximal adrenergic stimulation during the recordings. That is why a 2% adrenalin hydrochloride solution was used in the beginning. However, after the first studies were completed an article by Tarkkanen (77)

appeared showing that with a 2% solution the pressure reduction was not as great as with weaker solutions, a 0.5 - 1% adrenalin solution showing a maximal effect. Thus during the later trials a 1% adrenalin solution was used.

However, in the present study oral timolol, atenolol and propranolol in comparable doses all had additive hypotensive effects with adrenalin, whether the solution was 1% or 2% and thus the strength of the adrenalin solution does not seem to have been of major importance.

Adrenergic mechanism.

The mechanism by which adrenalin lowers the IOP has not been fully clarified. Adrenergic innervation and receptors are present both in the ciliary body and in the chamber angle (16-20), and the presence of catecholamines in the ciliary body has been demonstrated (21). However, the mode of action of adrenalin in lowering intraocular tension is still an open question.

A probable explanation have been offered by Townsend and Brubaker (74). Using fluorophotometry and tonography they analysed the effects of a single dose adrenalin in healthy volunteers. They found that the immediate effects were to raise the facility of outflow and to increase the rate of formation of aqueous humor. The net effect resulted in a lowering of the intraocular tension.

However, as alfa and beta agonists and antagonists have all been shown both to increase and to decrease the intraocular pressure (3;26), it is easier to cite references which increase the confusion than to clarify the mechanism of action of adrenalin on IOP.

Dose-response of beta-blockers on IOP.

Since the discovery by Phillips in 1967 (33) that propranolol lowered the IOP both the oral and the topical use of beta-blockers have been investigated.

In a study of systemic propranolol Wettrell (26) concluded that the IOP-lowering effect seemed to be dose-dependent and Takase (79) also demonstrated a dose-dependent effect for bupranolol.

In a study of topical timolol Zimmerman (45) found a dose-response relationship but with no further increase with concentrations greater than 0.5%. A dose-response relationship has also been demonstrated for topical atenolol and metoprolol (26;80). The investigation of nine different topical beta-blockers by Bonomi (34) supports the conclusions of Wettrell (26) that the other properties of the beta-blockers (such as membrane stabilizing effects, intrinsic sympathomimetic activity, or the selectivity in beta-receptor blocking), do not influence the hypotensive effect, but that only the beta-blockade is responsible for the IOP-lowering effect. In the study of Bonomi (34) comparisons of different concentrations also suggested a dose-response relationship.

The present study shows a significantly stronger hypotensive effect with a high oral dose of timolol than with a small one (study IV). This is more thoroughly investigated in study V, when a dose-response relationship is suggested. However, the additional hypotensive effects with doses over 5 mg/day are minimal, as the dose-response curve shows. This might be due to the choice of healthy volunteers with normal IOP as subjects, as previously explained on page 39.

Wettrell (26) analysed the dose-response curve for propranolol in

doses 20 - 80 mg daily in patients with ocular hypertension and showed a clear dose-response relationship. The mean IOP-reduction from 20 mg propranolol was about 15 - 25% of the previous pressure and each doubling of the dose produced a further decrease of only 3 - 5%. The reduction was greater in the group with the higher IOP, a fact that has been observed by others (81). Similar results were obtained with oral timolol in the present study.

Unfortunately there is no dose-response study comparing the IOP-effects of different oral beta-blockers. A systemic comparison of beta-blockade potency ratio, based on the inhibition of isoprenaline-induced tachycardia, showed timolol to be six times more potent than propranolol (69).

The timolol doses used in the present study (5 - 30 mg) should thus correspond to doses of 30 - 180 mg propranolol a day.

Thus it seems that, as was the case with topical timolol (45), the dose-response curve for the effects of oral beta-blockers on IOP flattens out, with little further reduction of IOP occurring after a certain dose.

In study I propranolol 80 mg a day was used and in study II atenolol 50 mg and propranolol 40 mg. Both drugs lowered the IOP significantly but in the single dose study (II) atenolol was slightly more effective, which is in agreement with the findings of Mac Donald (82).

With topical timolol in study II the hypotensive effect in healthy volunteers was highly significant.

In study III the design of the trial prevented any conclusions about the hypotensive effect of topical timolol. However, all the patients had

newly-detected glaucoma with unsatisfactorily high levels of IOP at the beginning of the trial, but after the pre-treatment period with timolol the majority achieved a satisfactory IOP.

Pupil size.

The analysis of the effects on pupil size (II) showed that topical timolol or oral propranolol alone did not increase the pupil size, while a slight increase was noted with atenolol. Zimmerman (45) found that topical timolol did not effect pupil size and Wettrell (26) found that neither oral propranolol nor atenolol had any significant effect.

When combined with adrenalin all the above mentioned beta-blockers showed a pupil dilatating effect. This is in agreement with Keates (40), who studied topical timolol and adrenalin in glaucoma patients and found a slight increase of the pupil size with that combination.

The changes in pupil size produced by adrenalin alone were not statistically significant.

As is known beta-receptor stimulation causes a relaxation of smooth muscle, while alfa-receptor stimulation causes a contraction (83). Therefore, blocking the beta-receptor-mediated relaxation of the pupil dilatation would result in a more marked effect of the alfa-receptor stimulation by adrenalin, resulting in an increased dilatation of the pupil.

Unlike other beta-blockers atenolol increased pupil size when used alone and had a greater effect than the other beta-blockers when used in combination with adrenalin. No explanation can be offered for this phenomenon.

Effects on pulse rate and blood pressure (II).

A slight but highly significant decrease of pulse rate and blood pressure was observed during treatment with oral atenolol and propranolol, which is not surprising. Similar observation have been noted before (26;82).

Topical timolol also had a slight but significant effect on pulse rate and blood pressure. This contrasts with the results of Zimmerman (45) and Moss (53), who found no change in the circulatory parameters. However, other studies of topical timolol have demonstrated a decrease of the pulse rate (38;42).

In study II an analysis of BP and PR effects was made but in the later investigations this was excluded because of the difficulties of keeping the study double-blind if notable reductions of BP and PR were observed.

SUMMARY

1. The IOP-effect of combining a beta-blocker and adrenalin can be both additive and antagonistic. The net result seems to depend on the degree of beta-blockade, being antagonistic with a strong beta-blockade and additive with a weak beta-blockade. The additive effect is present with both unselective and selective blockers.
2. The effect seems to be independent of the mode of administration, oral or topical.
3. The effect of oral timolol on IOP seems to show a dose-response relationship, but there is very little additional effect with doses greater than 5 mg.
4. The beta-blocker used have an additive dilatating effect on the pupil when combined with adrenalin.
A slight depressant effect on blood pressure and pulse rate was found with oral atenolol, propranolol and topical timolol.

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